REMARKS

Claims 1-30 are pending. Claims 1-5 and 30 are under examination. Without addressing the merits of the rejections set forth in the Office Action mailed September 15, 2010, Applicant has canceled claims 4 and 6-30 without prejudice to Applicant's right to pursue these claims in a related application. Claims 1 and 5 have been amended. Claims 31 and 32 have been added. Support for the amendments and new claims can found throughout the specification and the claims as filed. For example, support for the amendments to claim 1 and claim 5 can be found on page 20, lines 14-15; page 20, line 29; page 21, lines 6-12; page 13, lines 21-28; page 41, line 24 through page 42, line 3; page 16, lines 1-3; Example II and originally filed claims 1-5. Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested. Upon entry of the amendments, claims 1-3, 5 and 31-32 will be pending and under examination.

Interview Summary

Applicant would like to thank Examiner Lu and Supervising Examiner Nguyen for the courtesy of conducting the in-person interview on March 2, 2011 regarding the above-identified application. Applicant believes that all the issues from the Office Action and those raised for the first time during the interview have been addressed and resolved by the claim amendments and accompanying remarks.. Accordingly, reconsideration of the following rejections is respectfully requested.

Rejection Under 35 U.S.C. §112, First Paragraph – Enablement

The rejection of claims 1-5 and 30 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Reconsideration and withdrawal of the rejections are respectfully requested.

First, the Office asserts that step (d) of claim 1 does not require that the first population of target nucleic acids is specific nucleic acids and non-cleaved nucleic acids are generated after digesting the first population of target nucleic acids with an enzyme that selectively cleaves at the target sequences that are unmethylated. Page 5 of the Office Action issued September 15, 2010. For example, the Office asserts that if the enzyme used in the method is exonuclease I,

which is allegedly a 3' to 5' single strand exonuclease, when the first population of target nucleic acids comprises a double stranded DNA having a single stranded portion on its 3' end, cleaved nucleic acids are generated after digesting the first population of target nucleic acids. The Office asserts it is unclear how the presence of the first population comprising non-cleaved target nucleic acids generated by exonuclease I can indicate the presence of methylated target nucleic acids in the first population.

Applicant respectfully submits that the example enzyme cited by the Office, exonuclease I, is not methylation sensitive, i.e. cleaving unmethylated nucleic acids sequences, while not cleaving the same nucleic acid sequence when it is methylated. Applicants respectfully point out that step (b) in claims 1 and 5 recite that the enzyme selectively cleaves at unmethylated target sequences and the enzyme does not cleave at methylated target sequences. The subject application also teaches that the term "methylated target sequence," when used in reference to an enzyme that discriminately cleaves at the site of the target sequence, refers to target sequences for methylation regardless of methylation status, and is interchangeably referred to as "methylation target sequences." (see page 13, lines 21-24). The subject application also teaches that typically the discrimination is based on methylation blocking restriction such that methylation target sequences in non-methylated state are discriminately cleaved by the enzyme (see page 13, lines 25-27). The subject application also teaches that an exemplary enzyme useful in the claimed methods is Hpa II, which is methylation sensitive (see page 13, lines 27-28 and Example II). Thus, Applicant respectfully submits that one of skill in the art based on the disclosure of the subject application and the claims as written would have been able to practice the claimed methods at the time of the invention without undue experimentation.

Second, the Office asserts that because claims 4 and 5 do not require that a plurality of target probes only hybridize with non-cleaved target nucleic acids, it is allegedly unclear how to differentiate the non-cleaved target nucleic acids from cleaved target nucleic acids. Page 6 of the Office Action issued September 15, 2010. Applicant respectfully points out that the claim elements of claim 4 have been incorporated into claim 1 and claim 5 has been amended into independent form. Furthermore, presently pending claims 1 and 5 recite that the probes in step (d)(i) are contacted with immobilized non-cleaved target nucleic acids, thereby selectively forming a plurality of hybridization complexes between the immobilized non-cleaved target

nucleic acids and the probes. Moreover, the probes include a first region complementary to a first region of a non-cleaved target nucleic acid. Applicant submits one of skill in the art would have recognized that the probes can differentiate the non-cleaved target nucleic acids from cleaved target nucleic acids due to the presence of the first region, which allows for selective formation of hybridization complexes between the immobilized non-cleaved target nucleic acids and the probes. Thus, Applicant respectfully submits that one of skill in the art based on the disclosure of the subject application and the claims as written would have been able to practice the claimed methods at the time of the invention without undue experimentation.

The Office also asserts that claim 4 is allegedly unclear as to how detecting the presence of the probes can be used as an indication of the presence of methylated target nucleic acids as well as to how in claim 5 detecting the presence of amplicons can be used as an indication of the presence of methylated target nucleic acids. Applicant respectfully points out that claim 1 has been amended to recite "whereby the presence of said hybridization complexes indicates the presence of methylation in said target sequences." Furthermore, claim 5 has been amended to recite "whereby the presence of said amplicons is an indication of the presence of methylation in said target sequences." As discussed above, the selective formation of hybridization complexes between the immobilized non-cleaved target nucleic acids and the probes provides one of skill in the art when practicing the claimed methods the ability to differentiate the non-cleaved target nucleic acids from cleaved target nucleic acids because the hybridization complexes do not form with cleaved target nucleic acids. Thus, the presence of the hybridization complexes is a direct indication of the presence of methylation in the target sequences.

Third, the Office asserts that Msp I can cut both CpG methylated and unmethylated DNA sequences and it is allegedly unclear how Msp I can selectively cleave at the target sequences that are unmethylated as recited in claim 1 and how the digestions by Msp I can be blocked by methylation at cytosine. Without acquiescing to the correctness of the Office's assertion, and in an effort to further prosecution, Applicant has canceled claim 30 without prejudice. Thus, this aspect of the rejection has been rendered moot.

Based on the amendments and remarks above, and further based on the personal

interview on March 2, 2011 conducted with the Examiner and his supervisor, Applicant respectfully submits that claimed methods are fully enabled because one of skill in the art at the time of the invention could readily practice the claimed methods without undue experimentation. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 USC § 112, Second Paragraph

Claims 1-5 and 30 stand rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Item 8: The Office asserts that step (c) of claim 1 is vague and indefinite because it is allegedly unclear that the target nucleic acids are from a first population or a second population or both the first and second populations. Applicant respectfully points out that step (b) of claim 1 has been amended to recite that the cleaving of the population of target nucleic acids results in the formation of a second population of cleaved target nucleic acids labeled with a purification tag, with the proviso that the enzyme does not cleave at methylated target sequences thereby providing non-cleaved target nucleic acids. Additionally, step (c) of claim 1 has been amended to recite immobilizing at least non-cleaved target nucleic acids by said purification tag. Thus, Applicant respectfully submits that the claimed method clearly identifies that at least the non-cleaved target nucleic acids from the third population are immobilized by the purification tag.

Item 9: The Office asserts that the recitation of "said first population comprising non-cleaved target nucleic acid" in step (d) claim 1 lacks sufficient antecedent basis because step (a) only has the phrase "a first population of target nucleic acids" and does not contain "a first population comprising non-cleaved target nucleic acids." Applicant respectfully points out that claim 1, step (d) has been amended to recite "said non-cleaved target nucleic acids," and now has proper antecedent basis in step (b), which recites "thereby providing non-cleaved target nucleic acids." Thus, all the claim elements have proper antecedent basis.

Item 10: The Office asserts that claim 4 is vague and indefinite because it is allegedly unclear whether the target nucleic acid recited in step (e)(i) is from the immobilized target nucleic acids. Applicant respectfully points out that claim 1 has been amended to include the

elements of claim 4, and claim 4 has been canceled. Applicant further points out that claim 1, step (d), has been amended to recite detecting the presence of the non-cleaved target nucleic acids by contacting the immobilized non-cleaved target nucleic acids with a composition. Thus, Applicant respectfully submits that the claimed method clearly identifies that the detection step of claim 1 is directed to immobilized non-cleaved target nucleic acids.

Item 11: The Office asserts that claim 4 is vague and indefinite in view of step (e)(ii) because the source of a methylated target sequence is allegedly unclear. Applicant respectfully points out that claim 1 has been amended to include the elements of claim 4, which been canceled. Applicant further points out that claim 1 has been amended to recite in step (a) "providing a first population of double-stranded target nucleic acids labeled with a purification tag, wherein said target nucleic acids comprise potentially methylated target sequences." Thus, Applicant submits that the claimed method clearly identifies that the methylated sequences are from the first population of double-stranded target nucleic acids.

Item 12: The Office asserts claim 4 is vague and indefinite in view of step (f) because it is allegedly unclear whether or not the probe is from the hybridization complexes. Applicant respectfully points out that claim 1 has been amended to include the elements of claim 4, which has been canceled. Applicant further points out that claim 1, step (d) has been amended to recite "contacting said immobilized non-cleaved target nucleic acids with a composition having a plurality of target probes, thereby selectively forming a plurality of hybridization complexes between said immobilized non-cleaved target nucleic acids and said target probes." Thus, Applicant submits that the method of claim 1 clearly identifies that hybridization complexes form between the probes and the immobilized non-cleaved target nucleic acids.

Item 13: The Office asserts that claim 5 is vague and indefinite in view of step (i) because it is allegedly unclear whether or not the probe is from the hybridization complexes. Applicant respectfully points out that claim 5 has been amended into independent form. Furthermore, claim 5 recites, in step (d)(i), "contacting said immobilized non-cleaved target nucleic acids with a compositions having a plurality of target probes, thereby selectively forming a plurality of hybridization complexes between said immobilized non-cleaved target nucleic acids and said target probes." Thus, Applicant submits that the method of claim 5 clearly

identifies that hybridization complexes form between the probes and the immobilized non-cleaved target nucleic acids.

Item 14: The Office asserts that claim 30 is vague and indefinite because Msp I can allegedly cut both CpG methylated and unmethylated DNA sequences, while claim 1 requires that the enzyme selectively cleaves at the target sequences that are unmethylated. Thus, claims 1 and claim 30 allegedly do not correspond to each other. Without acquiescing to the correctness of the Office's assertion, and in a sincere effort to further prosecution, Applicant has canceled claim 30 without prejudice. Thus, this aspect of the rejection has been rendered moot by the cancelation of claim 30.

Item 15: The Office asserts that the recitation of "the digestion" in claim 30 has insufficient antecedent basis for the limitation. Applicant submits that this rejection has been rendered moot by the cancelation of claim 30.

Item 16: The Office asserts that claim 30 is vague and indefinite because it is allegedly unclear where a cytosine is located. Applicant submits that this rejection has been rendered moot by the cancelation of claim 30.

Based on the amendments and remarks above, and further based on the personal interview conducted with the Examiner and his supervisor on March 2, 2011, Applicant submits that the claims are sufficiently clear and definite to meet the requirements of 35 USC § 112, second paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Applicant estimates that a fee of $810.00 for a Request for Continued Examination, and a fee of $ 1,110.00 for the extension of time are due. The fees will be paid by EFS-Web at the time this paper is filed. Applicant believes that no other fees are due. However, please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Jones Day Deposit Account No. 50-3013, referencing our number 404571-999004 and please credit any excess fees to such deposit account.

Respectfully submitted,

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